REMARKS

Applicants again wish to sincerely thank the Examiner for the courtesy of the interview conducted on September 7, 2007, and for the Examiner's consideration given to this case to date. The Examiner will appreciate that the amendments herein substantially incorporate the Examiner's suggestions made during the telephonic interview.

Status of Claims

The subject application was originally filed with 24 claims. On August 14, 2006, Applicants filed a First Preliminary Amendment, amending the subject application to add claims 25-33. On March 5, 2007, the Office issued a Restriction Requirement. On April 5, 2007, Applicants provisionally elected, with traverse in part, to prosecute claims 25-33. Applicants cancelled claims 15-24 without prejudice. Applicants traversed the restriction with respect to claims 1-14 and, in the May 9, 2007 Office Action, the Office rejoined claims 1-14. In Applicants' Amendment in Response to the May 9, 2007 Office Action, Applicants cancelled claims 5 and 12-14 without prejudice and amended claims 1, 6, 25, and 31. In this RCE, Applicants amend claims 1, 6, 25, 29, 31, and 33. Accordingly, claims 1-4, 6-11, and 25-33 remain pending in the subject application.

Summary of Office Action

In the August 24, 2007 Final Office Action, the Office:

(1) rejected claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;

(2) rejected claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention;

(3) rejected claims 1-4, 7-14, 25, and 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike et al, Invest. Radiol. 2001, 36, 303-308 ("Leike")

in view of Torchilin et al., Biochim. Biophys. Acta 1996, 1279, 75-83 ("Torchilin") or Sachse et al., Invest. Radiol. 1997, 32, 44-50 ("Sachse"); and

(4) rejected claims 1-4, 6-11, and 25-32 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,676,928 issued to Klaveness et al. ("Klaveness") or U.S. Patent No. 6,217,849B1 issued to Tournier et al. ("Tournier") in view of Torchilin.

1. Rejection of claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants have amended claim 33. Claim 33, as amended, complies with the written description requirement. Applicants respectfully request that the Office withdraw the rejection of claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

2. Rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention.

Applicants have amended claim 31. Claim 31, as amended, particularly points out and distinctly claims the subject matter which Applicants regard as their invention. Applicants respectfully request that the Office withdraw the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention.

3. Rejection of claims 1-4, 7-14, 25, and 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike in view of Torchilin or Sachse.

As amended, claim 1 calls for sterically stabilized liposomes encapsulating one or more nonradioactive contrast-enhancing agents, wherein the sterically stabilized liposomes comprise

cholesterol, at least one phospholipid, and at least one phospholipid which is derivatized with a polymer chain, the sterically stabilized liposomes being less than 150 nanometers in average diameter.

Amended claim 25 calls for at least one first lipid or phospholipid; at least one second lipid or phospholipid which is derivatized with one or more polymers; and at least one sterically bulky excipient capable of stabilizing the sterically stabilized liposome; wherein the at least one sterically stabilized liposome is less than 150 nanometers in average diameter, and wherein the at least one nonradioactive contrast enhancing agent is encapsulated by the at least one sterically stabilized liposome.

To establish prima facie obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03. The combination of Leike (liposome size = 201 nm) and Sachse (liposome size = 204 nm) does not teach each and every element of amended claims 1 and 25. In particular, the combination of Leike and Sachse does not teach sterically stabilized liposomes have a size of less than 150 nm. In fact, just such an attempted combination led to a "drastic increase in vesicle size." (Sachse, p. 3).

With respect to the combination of Leike and Torchilin, Applicants respectfully disagree that Torchilin teaches the preparation of liposomes from a mixture of PC, cholesterol, and PEG-PE. In fact, Torchilin teaches the preparation of liposomes from a mixture of PC, cholesterol, PEG-PE, and DTPA. The two compositions are clearly distinct because the introduction of the radioactive tracer in Torchilin, In^{111}, is made possible through chelation—that is, attachment to the outside of the liposomes—via DTPA. As a result, Torchilin is able to maintain the small liposome sizes (i.e., 120-150 nm).

In the telephonic interview, the Examiner observed that Torchilin uses the term "incorporated" in several instances to describe the trans-chelation of In^{111} to DTPA. However, this term does not imply encapsulation of the radioactive Indium into the interior of the liposome:

> The method of preparation described in Torchilin involves the formation of liposomes from a mixture of PC, cholesterol, PEG-PE, and SA-DTPA. Such liposomes will necessarily exhibit the DTPA molecule on both the outside and inside of the liposome wall. However, when exposed to the In^{111}-citrate complex, only the external DTPA will be bound by the citrate, thus localizing the In^{111} on the outside of the liposome exclusively. The reason for this is the In^{111}-citrate is a large ionic species, thus bearing a net charge in solution, and possessing very low membrane diffusivity. Penetration of this material into the lipidic bilayer is practically impossible and, thus, the material is excluded from the interior of the liposome. In contrast, amended claims 1 and 25 call for encapsulation of nonradioactive contrast enhancing agent.

Declaration of Dr. Annanth Annapragada, Ph.D., at ¶ 3, attached hereto as **EXHIBIT 1**. (Emphasis added). The September 7, 2007 telephonic interview revealed the need for clarification on this technical point. As such, good and sufficient cause exists for the Declaration and the timing of its filing.

It must be remembered that "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02(VI). No motivation exists to combine Leike and Torchilin, when the references are taken as whole. See May 3, 2007 PTO Memorandum, at p. 2 ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed"). Indeed, Torchilin's radioactively labeled, DTPA-derivatized liposomes may very well render Leike's compositions inoperable, and vice-versa. It is well-settled that if a proposal for modifying a reference in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See In re Fritch, 972 F.2d 1260, 1265 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.").

In short, an artisan having common sense at the time of the invention would not have reasonably considered combining the liposomes prepared by Torchilin and designed to externally

chelate an In^{111} complex, with Leike, whose liposomes are intended not to be PEGylated and are intended to include nonradioactive contrast enhancing agent, to arrive at the subject matter of the claims at issue. Ex Parte Green, Appeal 20071271, decided June 12, 2007, citing KSR Int'l v. Teleflex Inc., 127 S. Ct. 1227 (2007).

Based on the foregoing, Applicants respectfully request that the Office withdraw the rejection of amended claim 1 and its directly or indirectly dependent claims 2-4 and 7-11, and amended claim 25 and its directly or indirectly dependent claims 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike in view of Torchilin or Sachse.

4. Rejection of claims 1-4, 6-11, and 25-32 under 35 U.S.C. § 103(a) as being unpatentable over Klaveness or Tournier in view of Torchilin.

As amended, claim 1 calls for, among other things, cholesterol. Claim 25 calls for a sterically bulky excipient (e.g., sterols such as cholesterol, fatty alcohols, or fatty acids). Klaveness does not teach cholesterol-containing or other sterically bulky excipient-containing liposomes of any size. Moreover, Klaveness' autoclaved compositions include contrast enhancing agent in the suspension medium.

Tournier teaches vesicles in the 200 nm to 1 μm range, with an average diameter of 400 nm. Tournier, col. 4, lines 60-67. Tournier explicitly and clearly teaches away from the use of "tiny" liposomes:

> The use of tiny liposome vesicles of the kind proposed in EP-A-0 442 962 for the delivery of drugs (in the order of 50 nm or less) ***are*** [sic] ***therefore unpractical*** for blood-pool imaging. Much the same applies to the proposals of Gabison et al. in Biochim. Et Biophys. Acta 1103 (1992) 94-100 and I.A.J.M. Bakker-Woudenberg et al. ibid 318-326 directed to liposomes with an average size between 0.07 μm and 0.1 μm and prolonged residence times in the blood.

Tournier, col. 3, lines 14-22 (emphasis added). Indeed, as explicitly noted by Tournier, at col. 5, line 66-col. 6, line 7:

> It is advantageous to use suspensions in which the vesicles have a size distribution as narrow as possible around a nominal value selected in the give 0.2 to 1.0 μm range and preferably in the range between 0.2 and 0.6 μm. For instance, if the selection desirably involves a suspension of vesicles of, say 0.4 μm, it is preferably that at least 80%, according to volume distribution, of the vesicle [sic] have a size of 0.4 μm±10%. The narrow width of the vesicle size distribution band can be considered here as a quality factor.

Tournier, col. 5, line 66-col. 6, line 7.

Applicants further respectfully disagree that Tournier discloses that liposome suspensions in the field of imaging are known to be about 100 nm in size. In fact, Tournier discloses that lipsome suspensions of that size are known to be used in drug delivery, but would be "unpractical for blood pool imaging." (Tournier, col. 3, lines 3-30). Applicants respectfully submit that Tournier's use of a round number (100 nm) in a normative calculation (col. 7, lines 36-46) may not fairly be said to mean that "liposome suspensions in the field of imaging are known to be about 100 nm in size." It should be noted that Tournier's normative calculation teaches that using such small vesicle sizes would lead to a viscosity that is too high to be considered useful. (Tournier col. 7, lines 46-47). Certainly, no indication exists that Tournier even contemplated a PEGylated liposome having such a tiny vesicle size.

Indeed, Tournier clearly disavows and teaches away from the use of polymer-derivatized phospholipids. See, e.g., col. 3, lines 30-35:

> ***[T]he production of liposomes with the "stealth factors" is rather cumborsome. In addition***, "stealth factored" liposomes are known to have very low entrapment capacity and while such liposomes may be suitable to carry specific drugs, and therefore useful in therapy, ***they are almost useless in imaging***.

Tournier, col. 3, lines 30-35 (emphasis added). See also, col. 3, lines 64-67:

> The blood pool agents contain liposomes with astounding so called "stealth" properties without requiring incorporation of the priorly recognized "stealth factors".

Tournier, col. 3, lines 64-67. See also, col. 5, lines 50-62:

> It is also noteworthy that the additional incorporation of the priorly recognised "stealth factors" into the liposomes and the suspensions of the invention (which are useful in other liposome formulations) will bring no further improvement in the "stealth" properties of the present suspensions. The incorporation of these factors into the liposomes will thus have insufficient impact on the residence time of the liposomes of the invention in the blood. Actually, ***the incorporation of recognized stealth factors to the formulations of the present liposomes suspensions may even be detrimental*** as the captured volume E_c (entrapped volume/weight of lipid) may be significantly reduced.

Tournier, col. 5, lines 50-62 (emphasis added).

Again, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.02(VI). Certainly, when Tournier is taken as a whole, it cannot be fairly said that the requisite motivation exists to combine Tournier with any reference to arrive at a composition having average vesicle sizes of less than 150 nm, which contain stealth factors such as PEG-PE.

It should be noted that Tournier, which was filed on June 25, 1997, represented the state of the art in the field of blood pool imaging at that time. In other words, Tournier's strong and clear disavowal of stealth factors and "small" liposomes, as outlined extensively in Applicants' Amendment in Response to the May 9, 2007 Office Action and above, had the benefit of the teachings of at least Sachse and Torchillin and still found stealth factors to be "useless in imaging" and small liposomes to be "unpractical."

In light of Tournier, the Office has not provided evidence that it was conventional in the art to use "small," PEGylated liposomes, encapsulating nonradioactive contrast enhancing agent, in the field of X-ray imaging.

Applicants refer to the above discussion regarding the inapplicability of Torchilin—when taken as a whole—to the subject application.

Based on the foregoing, Applicants respectfully request that the Office withdraw the rejection of amended claim 1 and its directly or indirectly dependent claims 2-4 and 6-11, and

amended claim 25 and its directly or indirectly dependent claims 26-32 under 35 U.S.C. § 103(a) as being unpatentable over Klaveness or Tournier in view of Torchilin.

CONCLUSION

Applicants sincerely appreciate the Examiner's time and careful consideration of this submission. In view of the remarks above and the amendments presented herein, it is believed that claims 1-4, 6-11, and 25-33, as amended, are in condition for allowance and notice to such effect is respectfully requested. If the Examiner thinks another telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at the phone number provided below.

If additional fees are due in connection with this Amendment, the Commissioner is authorized to charge Deposit Account No. 02-2051, identifying Docket No. 27428-4.

Respectfully submitted,

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